Supplement S 3. Model 1 equations and parameter estimates for all dopamine D_2 antagonists.

To describe dopamine and antagonist binding to the D_2-receptor, a simple drug-target binding model with competition between antagonist and dopamine was developed. This model assumed a constant total receptor concentration. This was represented as a single conservation equation of total receptor (R_t), where the receptor can have 3 different states: free receptor (R), antagonist bound to receptor (RL) and dopamine bound to receptor (RDA). Receptor recycling (RR) was added to this model as well, which describes internalization of the receptor-agonist complex, dissociation of this complex return of the free receptor to the cell membrane. This model is given by the following equations (equation 1-5):

$$\frac{d[L]}{dt} = -k_{onL}[R][L] + k_{offL}[RL]$$

(Eq. 1)

$$\frac{d[DA]}{dt} = -k_{onD}\ [R][DA] + k_{offDA}[RDA] + RR[RDA]$$

(Eq. 2)

$$\frac{\mathrm{d[RL]}}{\mathrm{dt}} = k_{onL}[R][L] - k_{offL}[RL]$$

(Eq. 3)

$$\frac{\mathrm{d[RDA]}}{\mathrm{dt}} = k_{onDA}[R][DA] - k_{offDA}[RDA] - RR[RDA]$$

(Eq. 4)

$$[R] = [R_t] - [RL] - [RDA]$$

(Eq. 5)

In these equations, [L] represents the free antagonist concentration, [DA] represents the free dopamine concentration, [R_t] represents the total receptor concentration, [R] represents the free receptor concentration, [RL] represents the concentration of the receptor—antagonist complex and [RDA] represents the concentration of the receptor—dopamine complex. k_{onL} and k_{onDA} represent the second-order association rate constants of receptor with the antagonist and with dopamine, respectively. k_{offL} and k_{offDA} represent the first order dissociation rate constants of the antagonist and dopamine from the receptor-bound complex, respectively. The receptor binding part of the model as described above was connected to cAMP concentrations in a mechanistic manner according to the following equations (equation 6 and 7).

$$\frac{d[cAMP]}{dt} = \left(k_1 + \frac{k_{0,max}[RL]^n}{EC50^n + [RL]^n}\right)\left(1 - \frac{[RDA]^n}{IC50^n + [RDA]^n}\right) - k_2[cAMP] - k_3[cAMP][PDE]$$

(Eq. 6)

Here, $k_{0,max}$ represents the maximum rate constant for inverse agonism by the receptor-antagonist complex, where n is the hill coefficient. Additionally, k_1 represents the rate constant for baseline synthesis of cAMP by adenylyl cyclase. Furthermore, the total cAMP synthesis is inhibited by the receptor dopamine complex (RDA) in a nonlinear manner, where n is the hill coefficient as well. k_2 is the rate constant for cAMP elimination independent of active PDE, and k_3 is the rate constant of active PDE-mediated cAMP elimination. active PDE synthesis is dependent on the cAMP concentration, and active PDE degradation is determined by the first order rate constant k_5 as in equation 7.

$$\frac{d[PDE]}{dt} = k_4[cAMP] - k_5[PDE]$$

(Eq. 7)

Table S 3. Parameter estimates from fitting the final model to the cAMP response data. Asterisks indicate parameter values that were not estimated but used as input parameter values. $DAFR_{50}$ denotes the ratio of the total receptor concentration divided by the dopamine-bound bound receptor concentration that inhibits the cAMP synthesis to 50%, LFR_{50} denotes the ratio of the total receptor concentration divided by the antagonist bound receptor concentration that generates the half-maximal antagonist-dependent cAMP synthesis (i.e. k_0 equals 0.5 * k_{0max}), R_{tot} denotes the total receptor concentration, k_{0max} denotes the maximal value of k_0.

Parameter (unit)	Value	RSE
k_{off} Bromperidol (min^{-1})	0.235*	
k_{off} Clozapine (min^{-1})	3.08*	
k_{off} Domperidone (min^{-1})	0.0322*	
k_{off} JNJ-39269646 (min^{-1})	10.7*	
k_{off} JNJ-37822681 (min^{-1})	0.573*	
k_{off} Haloperidol (min^{-1})	0.269*	
k_{off} Nemonapride (min^{-1})	0.0326*	
k_{off} Olazapine (min^{-1})	0.600*	
k_{off} Paliperidone (min^{-1})	0.211*	
k_{off} Pimozide (min^{-1})	0.0042*	
k_{off} Quetiapine (min^{-1})	1.01*	
k_{off} Raclopride (min^{-1})	0.0358*	
k_{off} Remoxipride (min^{-1})	1.89*	
k_{off} Risperidone (min^{-1})	0.199*	
k_{off} Sertindole (min^{-1})	0.141*	
k_{off} Spiperone (min^{-1})	0.0582*	
k_{off} Ziprasidone (min^{-1})	0.1*	
K_D Bromperidol (nM)	2.04	2%
K_D Clozapine (nM)	440	2.10%
K_D Domperidone (nM)	1.72	2.10%
K_D JNJ-39269646 (nM)	104	1.90%
K_D JNJ-37822681 (nM)	19.5	1.90%
K_D Haloperidol (nM)	1.72	2.40%
K_D Nemonapride (nM)	0.454	2.20%
K_D Olazapine (nM)	22.7	2.30%
K_D Paliperidone (nM)	1.61	2.40%
K_D Pimozide (nM)	291	2.80%
K_D Quetiapine (nM)	942	2.20%
K_D Raclopride (nM)	8.29	2.20%
K_D Remoxipride (nM)	118	2.70%
K_D Risperidone (nM)	10.5	4.60%
K_D Sertindole (nM)	6.89	2%
K_D Spiperone (nM)	0.19	2.50%
K_D Ziprasidone (nM)	3.56	1.80%
K_D Dopamine (nM)	10.3	3.90%
k_{off} Dopamine (min^{-1})	1.69*	
R_{tot} [D_2-Receptor concentration] (nM)	1.74	1.30%
k_{0max}: Maximum cAMP synthesis induced by inverse agonism AU (min^{-1})	20.5	0.50%

k_1: Baseline cAMP synthesis (AU min^{-1})	4.12	0.80%
k_2: cAMP degradation independent from active PDE (min^{-1})	0.0334	10.80%
k_3: cAMP degradation by active PDE (nM^{-1} min^{-1})	0.00882	0.20%
k_4: active PDE synthesis (min^{-1})	0.00882[a]	
k_5: active PDE degradation (min^{-1})	0.0005*	
$DAFR_{50}$ Dopamine	2.25	2.40%
Hill coefficient	1.77	0.40%
LFR_{50} Bromperidol	1.54	0.60%
LFR_{50} Clozapine	0.504	0.70%
LFR_{50} Domperidone	1.71	0.60%
LFR_{50} JNJ-39269646	0.856	0.50%
LFR_{50} JNJ-37822681	0.823	0.40%
LFR_{50} Haloperidol	0.699	0.50%
LFR_{50} Nemonapride	2.47	1.10%
LFR_{50} Olazapine	0.628	0.60%
LFR_{50} Paliperidone	0.657	0.50%
LFR_{50} Pimozide	618	1.90%
LFR_{50} Quetiapine	0.827	0.90%
LFR_{50} Raclopride	2.68	1.20%
LFR_{50} Remoxipride	1.95	1.40%
LFR_{50} Risperidone	5.37	3.60%
LFR_{50} Sertindole	1.02	0.50%
LFR_{50} Spiperone	1.56	0.60%
LFR_{50} Ziprasidone	0.959	0.40%
Receptor Turnover (min^{-1})	0.238	2.20%
Proportional error	0.01	0.30%

[a] k_4 was set to have the same value as k_3.